

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re application of:	)	Examiner: Saoud, Christine J.
	)	
Avi ASHKENAZI, <i>et al.</i>	)	Art Unit: 1647
	)	
Application Serial No. 09/905,348	)	Confirmation No: 3826
	)	
Filed: July 13, 2001	)	Attorney's Docket No. 39780-1618 P2C18
	)	
For: <b>SECRETED AND TRANSMEMBRANE</b>	)	<b>Customer No. 35489</b>
<b>POLYPEPTIDES AND NUCLEIC</b>	)	
<b>ACIDS ENCODING THE SAME</b>	)	

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**FILED VIA EFS  
ON SEPTEMBER 24, 2007**

**ON APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES**  
**APPELLANTS' BRIEF**

**MAIL STOP APPEAL BRIEF - PATENTS**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, Virginia 1813-1450

Dear Sir:

A Notice of Non-Compliance was mailed on August 23, 2007 in the above identified application. This amended Appeal Brief is timely filed hence no fees are believed due.

This Appeal Brief is responsive to the Final Office Action mailed on October 17, 2006. A Notice of Appeal was filed herein on March 19, 2007. Appellants request that the Evidence list filed with Appeal Brief of July 23, 2007 be appended to this reply. Appellants hereby appeal to the Board of Patent Appeals and Interferences from the final rejection in this case.

The following constitutes the Appellants' Brief on Appeal.

**I. REAL PARTY IN INTEREST**

The real party in interest is Genentech, Inc., South San Francisco, California, by an assignment of the parent application, U.S. Patent Application Serial No. 09/665,350 recorded July 9, 2001, at Reel 011964 and Frame 0181. The present application is a continuation of U.S. Patent Application Serial No. 09/665,350.

**II. RELATED APPEALS AND INTERFERENCES**

The claims pending in the current application are directed to a polypeptide referred to herein as "PRO232." Although there exist several applications directed to the "gene amplification" utility under Appeal, there are no applications related to PRO232 nucleic acids or antibodies.

**III. STATUS OF CLAIMS**

Claims 44-46 and 49-51 are in this application.

Claims 1-43 and 47-48 have been canceled.

Claims 44-46 and 49-51 stand rejected and Appellants appeal the rejection of these claims.

A copy of the rejected claims in the present Appeal is provided in Section IX.

**IV. STATUS OF AMENDMENTS**

A summary of the prosecution history for this case is as follows:

Previously, in response to a Final Office Action mailed on October 21, 2005, a Notice of Appeal was filed on February 21, 2006 and an Appeal Brief was filed on April 17, 2006. An RCE Response with additional references and affidavits supporting Appellants' arguments was filed on July 27, 2006. A Final Office Action was mailed on October 17, 2006, and a Notice of Appeal was filed on March 19, 2007.

No amendments were submitted after the final rejection mailed on October 17, 2006. All previous amendments have been entered.

**V. SUMMARY OF CLAIMED SUBJECT MATTER**

The invention claimed in the present application is related to an isolated polypeptide comprising the amino acid sequence of the polypeptide of SEQ ID NO:18, referred to in the

present application as “PRO232”. The PRO232 gene was shown for the first time in the present application to be significantly amplified in human lung cancers as compared to normal, non-cancerous human tissue controls (Example 92). This feature is specifically recited in Claim 124, and carried by all claims dependent from Claim 44. In addition, the invention also claims the amino acid sequence of the polypeptide of SEQ ID NO:18, lacking its associated signal-peptide; or the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209250 (Claims 44-46 and 49). The invention is further directed to a chimeric polypeptide comprising one of the above polypeptides fused to a heterologous polypeptide (Claim 50), and to a chimeric polypeptide wherein the heterologous polypeptide is an epitope tag or an Fc region of an immunoglobulin (Claim 51). The preparation of chimeric PRO polypeptides (Claims 50 and 51), including those wherein the heterologous polypeptide is an epitope tag or an Fc region of an immunoglobulin, is set forth in the specification at page 74, line 23 to page 75, line 5. Examples 53-56, pages 192-199, describe the expression of PRO polypeptides in various host cells, including *E. coli*, mammalian cells, yeast and Baculovirus-infected insect cells.

The amino acid sequence of the “PRO232” polypeptide and the nucleic acid sequence encoding this polypeptide (referred to in the present application as “DNA34435-1140”) are shown in the present specification as SEQ ID NOs: 18 and 17, respectively, and in Figures 9 and 8, described on page 59, lines 4-7. The full-length PRO232 polypeptide having the amino acid sequence of SEQ ID NO:18 is described in the specification at, for example, on page 4, pages 3-4 and page 100, page 131, lines 9 to 16 and the isolation of cDNA clones encoding PRO232 of SEQ ID NO:18 is described in Example 4, pages 149-150 of the specification. The specification discloses that the PRO232 polypeptide possess significant sequence homology to cell surface stem cell antigen (35% sequence identity with a stem cell surface antigen from *Gallus gallus*) and may play a role in cell proliferation and/or differentiation. (see for example, page 4 and Example 4, lines 14-15).

Finally, Example 92, in the specification at page 222, line 26, to page 235, line 3, sets forth a ‘Gene Amplification assay’ which shows that the PRO232 gene is amplified in the genome of certain human lung cancers (see Table 9, pages 230-234). The profiles of various primary lung and colon tumors used for screening the PRO polypeptide compounds of the

invention in the gene amplification assay are summarized on Table 8, page 227 of the specification.

## **VI. GROUND OF REJECTION TO BE REVIEWED ON APPEAL**

1. Whether instant Claims 44-46 and 49-51 satisfy the utility/enableness requirement under 35 U.S.C. §§101/112, first paragraph.
2. Whether Claims 44-46 and 49-51 are entitled to the priority date of U.S. Provisional Patent Application Serial No. 60/059121, filed September 17, 1997.
3. Whether Claims 44-46 and 49-51 are anticipated under 35 U.S.C. §102(b) by Rosenthal *et al.*, DE19818619-A1 (October 1999).

## **VII. ARGUMENTS**

### **Summary of the Arguments**

#### **Issue 1: Utility**

As a preliminary matter, Appellants note that the Examiner refers to the microarray assay in several instances in several Office Actions, and cites references like Lilley *et al.*, King *et al.*, Lee *et al.*, Wildsmith *et al.*, Chen *et al.* etc. which use and analyze the microarray assay. In addition, the Examiner rejects the use of the “universal control” in the instant application. Appellants point out that neither the “universal control” nor the microarray were used in the claimed invention, hence rejections directed either to the limitations of the use of the microarray assay, or to the universal control, are moot. On the other hand, Appellants rely upon the gene amplification data of the PRO232 gene for patentable utility of the PRO232 polypeptides in the present application, and controls defined in Example 92 of the instant specification, and would like to distinguish between the gene amplification and the microarray assay. The gene amplification assay measures the level at which a certain gene (*i.e.*, DNA) is amplified in the genome, whereas the microarray assay measures the level of expression of a mRNA encoding for a certain polypeptide in a sample. Throughout prosecution, the Examiner fails to distinguish between these two techniques, but Appellants submit that the two assays, although similar, are not the same.

Appellants would like to bring to the Examiner’s attention a recent decision in a microarray case by the Board of Patent Appeals and Interferences (Decision on Appeal

No. 2006-1469). In its decision, the Board reversed the utility rejection, acknowledging that “there is a strong correlation between mRNA levels and protein expression, and the Examiner has not presented any evidence specific to the PRO1866 polypeptide to refute that.” (Page 9 of the Decision). Appellants submit that, in the instant application, the Examiner has likewise not presented any evidence specific to the PRO232 polypeptide to refute Appellants’ assertion of a correlation between DNA levels, mRNA levels and protein expression. Appellants add that they discuss or analyze the microarray assay only in response to the Examiner’s citations and in response to correlation of mRNA and protein levels. This is not to be construed as an admission that all that applies to the microarray assay, applies to the gene amplification assay as well.

Appellants rely upon the gene amplification data of the PRO232 gene for patentable utility of the PRO232 polypeptides. The specification discloses that the gene encoding PRO232 showed significant amplification, ranging from 2.056-fold to 5.28-fold, in five lung tumors or 2.00-fold to 5.32-fold in seven colon tumors.

Appellants have submitted, in their Response filed on July 25, 2005, a Declaration by Dr. Audrey Goddard, which explains that a gene identified as being amplified at least 2-fold by the disclosed gene amplification assay in a tumor sample relative to a normal sample is useful as a marker for the diagnosis of cancer, and for monitoring cancer development and/or for measuring the efficacy of cancer therapy. Therefore, such a gene is useful as a marker for the diagnosis of lung or colon cancer, and for monitoring cancer development and/or for measuring the efficacy of cancer therapy.

Appellants have also submitted, in their Responses filed on August 9, 2004, and July 27, 2006, ample evidence to show that, in general, if a gene is amplified in cancer it is more likely than not that the encoded protein will be expressed at an elevated level. For instance, the articles by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* collectively teach that in general, gene amplification increases mRNA expression. Second, the Declarations of Dr. Paul Polakis: (Polakis I and II), shows that, in general, there is a correlation between mRNA levels and polypeptide levels. Third, Appellants further submit that even if there were no correlation between gene amplification and increased mRNA/protein expression, (which Appellants expressly do not concede to), a polypeptide encoded by a gene that is amplified in cancer would still have a specific, substantial, and credible utility. Appellants submit that, as evidenced by the

Ashkenazi Declaration and the teachings of Hanna and Mornin (both made of record in Appellants' Responses filed on December 10, 2003 and August 9, 2004), simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy for the tumor, as demonstrated by a real-world example of the breast cancer marker HER-2/neu.

Appellants further note that the sale of gene expression chips to measure mRNA levels is a highly successful business, with a company such as Affymetrix recording 168.3 million dollars in sales of their GeneChip arrays in 2004. Clearly, the research community believes that the information obtained from these chips is useful (*i.e.*, that it is more likely than not informative of the protein level). Therefore, as a general rule, one skilled in the art would find it more likely than not that PRO232 polypeptides are useful as a diagnostic tools for detecting lung or colon tumors.

The Examiner relies on the teachings of Pennica *et al.*, Konopka *et al.*, Haynes *et al.*, Hu *et al.*, Lian *et al.*, Fessler *et al.*, Gygi *et al.*, Lilley *et al.*, Lee *et al.*, King *et al.*, Wildsmith *et al.*, Nagaraja *et al.*, Sagynaliev *et al.*, Waghray *et al.*, Madoz-Gurpide *et al.*, Feroze-Merzoug *et al.*, Bustin *et al.*, Saito-Hisaminato *et al.*, to allege that there is no correlation between increased gene amplification and protein levels.

Appellants respectfully disagree and submit that the teachings within these cited references do not conclusively establish a *prima facie* case for lack of utility because the references are, either not contrary to the Appellants' arguments, or, actually lend support to the Appellants' position, or, are not applicable to the present application for various reasons, as discussed in detail below. On the other hand, Appellants submit that while the literature indicates that some references demonstrate a positive correlation between DNA levels, mRNA expression and protein levels, and some show no correlation, in general, there are more cases in literature that show a positive correlation than not.

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology that there is generally a positive correlation between DNA, mRNA, and polypeptide levels, in general, in the majority of amplified genes, as exemplified by the teachings of Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, the two Polakis

Declarations, the art overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. The widespread, art accepted use of information obtained from array chips for detecting diagnostic markers lend further support that in general, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO232 gene, that the PRO232 polypeptide is concomitantly overexpressed and has utility in the diagnosis of lung or colon cancer or for individuals at risk for developing lung or colon cancer.

Accordingly, Appellants submit that when the proper legal standard is applied, one should reach the conclusion that the present application discloses at least one patentable utility for the claimed PRO232 polypeptides. Accordingly, one of ordinary skill in the art would also understand how to make and use the recited polypeptides for the diagnosis of lung or colon cancer without any undue experimentation.

### **Issue 2: Priority**

The instant application has not been granted the earlier priority date of U.S. Provisional Patent Application Serial No. 60/059121, filed September 17, 1997 on the grounds that the 60/059121 application fails to provide a utility and lacks an enabling disclosure for the claimed invention under 35 U.S.C. §§101/112, first paragraph.

Appellants submit that, for the same reasons discussed above under Issue 1, U.S. Provisional Patent Application Serial No. 60/059121 also satisfies the utility requirements. Therefore, Appellants should be entitled to the priority date of **September 17, 1997**.

### **Issue 3: Anticipation by Rosenthal *et al.***

As discussed above under Issue 2, the present application should be entitled to the earlier filing date of **September 17, 1997** and therefore, Rosenthal *et al.*, DE19818619-A1, dated October 1999, is not prior art. Thus the instant claims are not anticipated by Rosenthal *et al.*

These arguments are all discussed in further detail below under the appropriate headings.

## Response to Rejections

### ISSUE 1: The Instant Claims 44-46 and 49-51 Satisfy the Utility Requirement under 35 U.S.C. §101/§112, First Paragraph, based on the results of the gene amplification assay

The sole basis for the Examiner's rejection of Claims 44-46 and 49-51 under this section is that the data presented in the instant Application, allegedly, does not satisfy the requirements of 35 U.S.C. §§101/112, first paragraph. Appellants strongly disagree for the reasons discussed below.

#### **A. The Legal Standard For Utility Under 35 U.S.C. §101**

According to 35 U.S.C. §101:

Whoever invents or discovers any new and *useful* process, machine, manufacture, or composition of matter, or any new and *useful* improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.  
(Emphasis added.)

In interpreting the utility requirement, in *Brenner v. Manson*,<sup>1</sup> the Supreme Court held that the *quid pro quo* contemplated by the U.S. Constitution between the public interest and the interest of the inventors required that a patent applicant disclose a "substantial utility" for his or her invention, *i.e.*, a utility "where specific benefit exists in currently available form."<sup>2</sup> The Court concluded that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. A patent system must be related to the world of commerce rather than the realm of philosophy."<sup>3</sup>

Later, in *Nelson v. Bowler*,<sup>4</sup> the C.C.P.A. acknowledged that tests evidencing pharmacological activity of a compound may establish practical utility, even though they may not establish a specific therapeutic use. The Court held that "since it is crucial to provide researchers with an incentive to disclose pharmaceutical activities in as many compounds as

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<sup>1</sup> *Brenner v. Manson*, 383 U.S. 519, 148 U.S.P.Q. (BNA) 689 (1966).

<sup>2</sup> *Id.* at 534, 148 U.S.P.Q. (BNA) at 695.

<sup>3</sup> *Id.* at 536, 148 U.S.P.Q. (BNA) at 696.

<sup>4</sup> *Nelson v. Bowler*, 626 F.2d 853, 206 U.S.P.Q. (BNA) 881 (C.C.P.A. 1980).



possible, we conclude adequate proof of any such activity constitutes a showing of practical utility.”<sup>5</sup>

In *Cross v. Iizuka*,<sup>6</sup> the C.A.F.C. reaffirmed *Nelson*, and added that *in vitro* results might be sufficient to support practical utility, explaining that “*in vitro* testing, in general, is relatively less complex, less time consuming, and less expensive than *in vivo* testing. Moreover, *in vitro* results with the particular pharmacological activity are generally predictive of *in vivo* test results, *i.e.*, there is a reasonable correlation there between.”<sup>7</sup> The Court perceived, “No insurmountable difficulty” in finding that, under appropriate circumstances, “*in vitro* testing, may establish a practical utility.”<sup>8</sup>

The case law has also clearly established that Appellants’ statements of utility are usually sufficient, unless such statement of utility is unbelievable on its face.<sup>9</sup> The PTO has the initial burden to prove that Appellants’ claims of usefulness are not believable on their face.<sup>10</sup> In general, an Applicant’s assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, “unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.”<sup>11, 12</sup>

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<sup>5</sup> *Id.* at 856, 206 U.S.P.Q. (BNA) at 883.

<sup>6</sup> *Cross v. Iizuka*, 753 F.2d 1047, 224 U.S.P.Q. (BNA) 739 (Fed. Cir. 1985).

<sup>7</sup> *Id.* at 1050, 224 U.S.P.Q. (BNA) at 747.

<sup>8</sup> *Id.*

<sup>9</sup> *In re Gazave*, 379 F.2d 973, 154 U.S.P.Q. (BNA) 92 (C.C.P.A. 1967).

<sup>10</sup> *Ibid.*

<sup>11</sup> *In re Langer*, 503 F.2d 1380,1391, 183 U.S.P.Q. (BNA) 288, 297 (C.C.P.A. 1974).

<sup>12</sup> *See also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (C.C.P.A. 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (C.C.P.A. 1977).

Compliance with 35 U.S.C. §101 is a question of fact.<sup>13</sup> The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration.<sup>14</sup> Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

The well established case law is clearly reflected in the Utility Examination Guidelines (“Utility Guidelines”),<sup>15</sup> which acknowledge that an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted “specific, substantial, and credible utility” or a “well-established utility.” Under the Utility Guidelines, a utility is “specific” when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that are to be diagnosed.

In explaining the “substantial utility” standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase “immediate benefit to the public” or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be “currently available” to the public in order to satisfy the utility requirement. “Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a ‘substantial’ utility.”<sup>16</sup> Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement,<sup>17</sup> gives the following instruction to

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<sup>13</sup> *Raytheon v. Roper*, 724 F.2d 951, 956, 220 U.S.P.Q. (BNA) 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984).

<sup>14</sup> *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d (BNA) 1443, 1444 (Fed. Cir. 1992).

<sup>15</sup> 66 Fed. Reg. 1092 (2001).

<sup>16</sup> M.P.E.P. §2107.01.

<sup>17</sup> M.P.E.P. §2107 II (B)(1).

patent examiners: “If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility.”

**B. Proper Application of the Legal Standard**

Appellants respectfully submit that the data presented in Example 92 starting on page 222 of the priority application and the cumulative evidence of record, which underlies the current dispute, indeed support a “specific, substantial and credible” asserted utility for the presently claimed invention.

Patentable utility for the PRO232 polypeptides is based upon the gene amplification data for the gene encoding the PRO232 polypeptide. Example 92 describes the results obtained using a very well-known and routinely employed polymerase chain reaction (PCR)-based assay, the TaqMan<sup>TM</sup> PCR assay, also referred to herein as the gene amplification assay. This assay allows one to quantitatively measure the level of gene amplification in a given sample, say, a tumor extract, or a cell line. It was well known in the art at the time the invention was made that gene amplification is an essential mechanism for oncogene activation. Appellants isolated genomic DNA from a variety of primary cancers and cancer cell lines that are listed in Table 9 (pages 222 onwards of the specification), including primary lung and colon cancers of the type and stage indicated in Table 8 (page 227). The tumor samples were tested in triplicates with Taqman<sup>TM</sup> primers and with internal controls, beta-actin and GADPH in order to quantitatively compare DNA levels between samples (page 229). As a negative control, DNA was isolated from the cells of ten normal healthy individuals, which was pooled and used as a control (page 222, lines 28-29). The results of TaqMan<sup>TM</sup> PCR are reported in  $\Delta$ Ct units, as explained in the passage on page 222, lines 37-39. One unit corresponds to one PCR cycle or approximately a 2-fold amplification, relative to control, two units correspond to 4-fold, 3 units to 8-fold amplification and so on. Using this PCR-based assay, Appellants showed that the gene encoding for PRO232 was amplified, that is, it showed approximately 1.04-2.40  $\Delta$ Ct units for five lung tumors and 1.00-2.41  $\Delta$ Ct units for seven colon tumors, which corresponds to  $2^{1.04}$ - $2^{2.40}$ - fold amplification in lung or to  $2^{1.00}$ - $2^{2.41}$ - fold amplification in colon tumors; that is **2.056-fold to 5.28-fold in five lung tumors** or **2.00-fold to 5.32-fold in seven colon tumors**, which would be

considered significant and credible by one skilled in the art. Therefore, the PRO232 gene and the PRO232 polypeptide are important diagnostic markers to identify such malignant lung or colon cancers.

**A prima facie case of lack of utility has not been established**

As discussed above, the increase in DNA copy number for the PRO232 gene is significant. Further, the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility.

Accordingly, it is not a legal requirement to establish a necessary correlation between an increase in the copy number of the DNA and protein expression levels that would correlate to the disease state or that it is imperative to find evidence that DNA amplification is "necessarily" or "always" associated with overexpression of the gene product. Appellants respectfully submit that when the proper evidentiary standard is applied, a correlation must be acknowledged. Only after the Examiner has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the Applicant.

Previously, the Examiner has indicated based on references Pennica *et al.*, Konopka *et al.* and Haynes *et al.* to show that gene amplification data cannot reliably predict protein levels. Appellants have argued the references in great detail throughout prosecution and these arguments are incorporated by reference herein for brevity. Appellants summarize the rejections and the arguments submitted below.

The teachings of Pennica *et al.* are specific to *WISP* genes, a specific class of closely related molecules. Pennica *et al.* showed that there was good correlation between DNA and mRNA expression levels for the *WISP-1* gene, but not for *WISP-2* and *WISP-3* genes. *WISPs* 1-3 have no structural relationship to the PRO232 polypeptides of the present application. The apparent finding that for two out of three specific molecules, that are related to each other but have no relationship to PRO232, that there was no correlation between gene amplification and the level of mRNA/protein expression does not establish, in general, that it is more likely than not that such correlation does not exist, and has no bearing whatsoever on determining the

question whether such correlation is likely to exist between PRO232 gene amplification and mRNA/protein expression levels. As discussed above, the standard is not absolute certainty. Pennica *et al.* has no teaching whatsoever about the correlation of gene amplification and protein expression for genes in general, or PRO232 or related molecules in particular.

Similarly, in Konopka *et al.*, the Examiner has generalized a very specific result disclosed by Konopka *et al.* to cover all genes. Konopka *et al.* actually state that “[p]rotein expression is not related to amplification of the *abl* gene but to variation in the level of *bcr-abl* mRNA produced from a single Ph<sup>1</sup> template.” (See Konopka *et al.*., Abstract, emphasis added). The paper does not teach anything whatsoever about the correlation of protein expression and gene amplification in general, and provides no basis for the generalization that apparently underlies the present rejection. The statement of Konopka *et al.* that “[p]rotein expression is not related to amplification of the *abl* gene . . .” is not sufficient to establish a *prima facie* case of lack of utility. Therefore, the combined teachings of Pennica *et al.* and Konopka *et al.* are not directed towards genes in general but to a single gene or genes within a single family and thus, their teachings cannot support a general conclusion regarding a correlation between gene amplification and mRNA or protein levels. In addition, the *abl* gene has no structural relationship to the PRO232 gene of the present application and thus, Konopka *et al.* provides no information of specific relevance to the question whether for PRO232 there is a reasonable expectation that correlation between gene amplification and mRNA/protein expression levels is likely to exist.

The Examiner also cited Haynes *et al.* to show that transcript levels and protein levels do not correlate. However, Appellants had shown that Haynes themselves admit that “there was a general trend, although no strong correlation between protein [expression] and transcript levels.” (See Figure 1 and page 1863, paragraph 2.1, last line). Therefore, when the proper legal standard is used, Haynes clearly supports the Appellants' position that in general, a positive correlation exists between mRNA and protein expression levels. Since accurate prediction is not the standard, a *prima facie* case of lack of utility has not been met based on the cited references Pennica *et al.*, Konopka *et al.* and Haynes *et al.* Appellants respectfully submit that, contrary to the Examiner's assertion, none of the cited reference conclusively establish a *prima facie* case for lack of utility for the PRO232 molecule.

Appellants have already discussed references Hu *et al.*, Chen *et al.*, Lian *et al.*, Fessler *et al.*, in great detail in their previous responses (at least see Appeal Brief filed April 17, 2006), and **these arguments are hereby incorporated by reference for brevity.**

Briefly, the analytical methods utilized by Hu *et al.* have certain statistical drawbacks, as the authors themselves admit, and Hu *et al.*'s conclusions only apply to a specific type of breast tumor (estrogen receptor (ER)-positive breast tumor) and cannot be generalized to breast cancer genes in general, let alone to cancer genes in general.

Regarding Lian *et al.*, Appellants respectfully submit that Lian *et al.* only teach that protein expression may not correlate mRNA level in differentiating myeloid cells, and not about genes in general. In fact, the authors themselves admit that there were a number of problems with their data. For instance, at page 520 of this article, the authors explicitly express their concerns regarding the methods they utilized and the interpretation of their data stating that "[t]hese data must be considered with several caveats: membrane and other hydrophobic proteins and very basic proteins are not well displayed by the standard 2DE approach, and proteins presented at low level will be missed. In addition, to simplify MS analysis, we used a Coomassie dye stain rather than silver to visualize proteins, and this decreased the sensitivity of detection of minor proteins." (Emphasis added). Besides, Lian *et al.*'s conclusions are based on the Coomassie dye staining method, which is not a very sensitive method of measuring protein. Similarly, in Fessler *et al.*, examined lipopolysaccharide-activated neutrophilins, in response to LPS stimulation. Fessler *et al.* also used the Coomassie Blue dye staining method, and concede that it is known to have a limited protein binding range and a non-linear curve for protein detection. Protein identification in their study was also done using two-dimensional PAGE, which is, by their own admission, limited only to well-resolved regions of the gel, and therefore, may have performed less well with hydrophobic and high molecular weight proteins. (See page 31301, col. 1).

**Gygi et al.**

The Examiner has cited new reference Gygi *et al.* in the Final Office Action of October 17, 2006 addressing the correlation between mRNA and protein levels.

Appellants submit that Gygi *et al.* never indicate that the correlation between mRNA and protein levels does not exist. Gygi *et al.* only state that the correlation may not be sufficient to **accurately** predict the protein level from the level of the corresponding mRNA transcript. (See page 1270, Abstract). Gygi *et al.* may teach that protein levels cannot be “predicted” from mRNA levels in the sense that the exact numerical amounts of protein present in a tissue cannot be determined based upon mRNA levels. But Appellants respectfully submit that the PTO’s emphasis on the need to “accurately predict” protein levels based on mRNA levels misses the point. The asserted utility for the claimed polypeptides is in the diagnosis of cancer. What is relevant to use as a cancer diagnostic is relative levels of gene or protein expression, not absolute values, that is, that the gene or protein is differentially expressed in tumors as compared to normal tissues.

Moreover, contrary to the Examiner's statement, the Gygi data indicate **a general trend** of correlation between protein [expression] and transcript levels. (Emphasis added). For example, as shown in Figure 5, the mRNA abundance of **250-300** copies/cell correlates with the protein abundance of **500-1000** x 10<sup>3</sup> copies/cell. The mRNA abundance of **100-200** copies/cell correlates with the protein abundance of **250-500** x 10<sup>3</sup> copies/cell. (Emphasis added). Therefore, high levels of mRNA **generally** correlate with high levels of proteins. In fact, most data points in Figure 5 did not deviate or scatter away from the general trend of correlation. Thus, the Gygi data meets the “more likely than not standard” and shows that a positive correlation exists between mRNA and protein.

In summary, Hu *et al.*, Lian *et al.*, Fessler *et al.*, Gygi *et al.* do not conclusively teach that, in general, protein levels cannot be accurately predicted from mRNA/gene amplification levels. These authors concede that either due to insensitive protein detection methods or due to their methodologies utilized in their protocols, some protein species may have been under-represented over others. Therefore, the teachings of these references cannot be relied upon to establish a *prima facie* showing of lack of utility. On the other hand, as noted even in Haynes *et*

*al.* and Gygi *et al.* most genes showed a positive correlation between increased gene amplification, mRNA and translated protein.

The Examiner asserts that, of the references cited by Appellants in their IDS filed on July 27, 2006, “only Godbout *et al.* is pertinent.”

Appellants respectfully submit that, as discussed in the RCE response of July 27, 2006, there are several other references; for instance, Bea *et al.* who investigated gene amplification, mRNA expression, and protein expression of the putative oncogene BMI-1 in human lymphoma samples, and support Appellants’ assertion that gene amplification is correlated with both increased mRNA and protein expression.

**Godbout *et al.* (Item 46 of Evidence List)**

Regarding the Godbout reference, the Examiner alleges that the instant specification does not teach structure/function analysis; the Examiner says that she finds no reason to suspect if PRO232 can confer selective advantage to a cell. The Examiner questions whether the level of genomic amplification of DDX1 gene is comparable to that of PRO232. (Page 5 of Final Office Action of October 17, 2006).

Appellants respectfully submit that it was never claimed that PRO232 is similar in any way to the DDX1 gene of Godbout *et al.*, they never claimed PRO232 was an RNA helicase or that it confers selective advantage to cell survival; on the other hand, the Godbout reference was submitted to show good correlation between protein levels based upon genomic DNA amplification, which the Examiner clearly agrees with. Moreover, selective advantage to cell survival is not the only mechanism by which genes impact cancer and structure/function data, which the Examiner requests, is not a requirement for the utility requirement. Hence a *prima facie* case has not been established and this rejection is improper.

**Saito- Hisaminato *et al.* and Bustin *et al.***

The Examiner refers to the microarray assay and the “universal control” and indicates that proper controls are needed for the microarray assay. The Examiner rejects the use of the universal control based on the teachings within Saito- Hisaminato *et al.* (Pages 18-19 of the instant Final Office Action). The Examiner further cites Bustin *et al.* without any explanations for the citation.



As discussed above under Section VII, Appellants respectfully submit that they rely upon the gene amplification data of the PRO232 gene for patentable utility of the PRO232 polypeptides in the present application, not the microarray assay. Appellants would like to distinguish between the gene amplification and the microarray assay. The gene amplification assay measures the level at which a certain gene (*i.e.*, DNA) is amplified in the genome, whereas the microarray assay measures the level of expression of a mRNA encoding for a certain polypeptide in a sample. Throughout prosecution, the Examiner fails to distinguish between these two techniques, but Appellants submit that the two assays, although similar, are not the same. Any rejection directed to the limitations of the microarray assay or to the universal control are moot and are not addressed here. Only relevance of microarray array results to correlate mRNA to protein levels is discussed.

No “universal control” was used in the instantly claimed invention. Since “Saito-Hisaminato” primarily discusses the universal control, its teachings do not apply to the instant invention in any manner and is moot.

The Examiner has not provided reasons for why Bustin *et al.*, which uses and analyzes microarray technology, was cited. Without conceding to the propriety of this rejection, Appellants note that Bustin *et al.* do not dispute the use of microarrays to obtain biologically relevant data, noting that “several microarray experiments have generated clinically relevant quantitative gene profiles.” (Page 271, col. 1). In fact, Bustin *et al.* conclude that “[m]icroarrays are already having a major impact on cancer biology, pharmacology and drug development” and state that “the major limiting factor in their further application is the current lack of data comparability, which is essential for appropriate comparisons between different arrays.”

Accordingly, a *prima facie* case has not been established based on Saito- Hisaminato *et al.* and Bustin *et al.* and this rejection is improper.

**Lilley *et al.*, King *et al.*, Lee *et al.* and Wildsmith *et al.***

First of all, the references Lilley *et al.*, King *et al.*, Lee *et al.* and Wildsmith *et al.* all utilize and analyze the microarray assay. The Examiner cites the Lee *et al.* reference allege a limitation that requires replication of microarray assays. (See page 14, line 3 of Final Office Action). The Examiner cites King *et al.* to allege a limitation that microarray has variability for

high- or medium- abundance mRNAs. (See page 14, lines 12-13 of Final Office Action). The Examiner further indicates, based on Lilley *et al.*, Wildsmith *et al.*, and King *et al.*, that the state of the art demonstrates that correlation between mRNA and protein abundance “cannot be accurately predicted.” (Page 12 of Final Office Action).

Again, as discussed above, without conceding to the propriety of the rejections stated above, Appellants submit that the rejections directed to the limitations of microarray assay are moot and are not addressed here, since Appellants rely upon the gene amplification data of the PRO232 gene for patentable utility of the PRO232 polypeptides and not the microarray assay.

Appellants add that it is not a legal requirement for utility, to establish a necessary correlation between an increase in the mRNA level and protein expression levels; that is, the utility standard is not absolute certainty or it is not necessary to show that changes in transcript level should always result in corresponding changes in protein amount or activity. Accordingly, the question is not whether a correlation between an increase in mRNA and protein expression levels always exists, rather, if it is more likely than not to exist, and whether a person of ordinary skill in the pertinent art would recognize such a positive correlation.

Nowhere in the Lilley, Wildsmith or the King papers do the authors suggest that it is more likely than not that altered mRNA levels does not correlate with altered protein levels. In fact, the King reference discussed numerous advantages of the microarray technology, which offers tremendous advantages in the study of human diseases. For instance, on page 2287, the author states that “microarrays can be expected to prove extremely valuable as tools for the study of the generic basis of complex diseases. The ability to measure expression profiles across entire genomes provides a level of information not previously attainable..... Microarrays make it possible to investigate differential gene expression in normal vs. diseased tissue, in treated vs. non-treated tissue, and in different stages during the natural course of the disease, all on a genomic scale. Gene expression profiles may help to unlock the molecular basis of phenotype, response to treatment, and heterogeneity of disease.....” Therefore, if anything, the King reference supports the use of the microarray in the diagnosis of human diseases, which silently assumes that, most probably, increases in mRNA levels correlate well with increases in protein levels which in turn impacts disease.

Similarly, the Wildsmith paper discusses examples of a number of successes of microarray applications in the detection of human diseases. (See page 284). For instance, the author points out that “one area of rapid progress using microarray technology is the increased understanding of cancer. Molecular pathologies are subgrouping cancers of tissues such as blood, skin, and breast, based on differential gene expression patterns. For example, within a small group of breast cancer tissue samples, Perou *et al.* distinguished two broad subgroups representing those expressing or alternatively lacking expression of the oestrogen receptor-  $\gamma$ -gene. The work was not conclusive, but never has progress in this field been so rapid when compared with the previous methods of gene amplification. Another example of the impact of this technology is in the identification of two biomarkers for prostate cancer, namely hepsin and PIM1 (Dhanasekaran *et al.*, 2001). Microarray technology has also accelerated the understanding of the molecular events surrounding pulmonary fibrosis. Specially, two distinct clusters of genes associated with inflammation and fibrosis have been identified in a disease where, for years, the pathogenesis and treatment have remained unknown (Katsuma *et al.*, 2001).”

Therefore, contrary to the Examiner’s position regarding the Lilley *et al.*, Lee *et al.*, Wildsmith *et al.*, and King *et al.* references, collectively, the references show that the art indicates that, generally, if a mRNA is overexpressed in cancer, it is more likely than not that the encoded protein will also be expressed at an elevated level.

**Madoz Gurpide *et al.* and Feroze-Merzoug *et al.***

Again, the Examiner cites Madoz-Gurpide *et al.* and Feroze-Merzoug *et al.* to show that one cannot accurately predict protein levels based on mRNA levels (made of record by the Examiner in the Final Office Action mailed October 17, 2006).

Appellants respectfully disagree. Madoz-Gurpide *et al.* explains that mRNA expression alone does not provide information regarding the “**activation state, post-translational modification or localization of corresponding proteins.**” (Emphasis added; page 168, col. 1). That is, Madoz-Gurpide *et al.* explain that mechanisms are not apparent from mRNA expression alone. Madoz Gurpide *et al.* further state that, it is “unclear” how **well** the reported RNA levels correlate with protein levels. In support of this assertion, the authors cite only a single reference,

namely, the Chen *et al.*, which was discussed above and in detail in the Appeal Brief filed on April 17, 2006. Madoz Gurpide *et al.* also acknowledge that the DNA microarray studies, such as those carried out by Beer *et al.* (specifically cited by the authors at page 52), “**justify the use of this technology for uncovering patterns of gene expression that are clinically informative.**” (Emphasis added; page 53). Thus, while Madoz-Gurpide *et al.* note that it is “more difficult to develop an **understanding of disease** at a mechanistic level using DNA microarrays,” (emphasis added; page 53), Appellants respectfully point out that that “understanding of a disease at the mechanistic level” is not relevant to Appellants’ assertions of utility, as discussed above. Accordingly, a *prima facie* case cannot be made based on the teachings within the Madoz-Gurpide *et al.* reference.

Similarly, Feroze-Merzoug *et al.* appear to mainly focus on “accurately predicting” the precise levels of protein expression, which is not required for utility as a cancer diagnostic, as discussed above. Moreover, the teachings of Feroze-Merzoug *et al.* are directed specifically to androgen regulated genes, which clearly involve different biological processes than those involved in tumor development. Feroze-Merzoug *et al.* are not directed to genes in general, either, and hence this reference cannot be relied upon to establish a *prima facie* case for lack of utility.

**Nagaraja *et al.*, Waghray *et al.* and Sagynaliev *et al.***

Again, new references Nagaraja *et al.*, Waghray *et al.* and Sagynaliev *et al.* all utilize and analyze the microarray assay. Any rejection directed to the limitations of the microarray assay or to the universal control are moot and are not addressed here. Only relevance of microarray array results to correlate mRNA to protein levels is discussed.

The Examiner asserts that “[c]omprehensive studies where significantly large numbers of transcripts and proteins were examined report that increases in mRNA and protein samples are not correlated.” (Final Office Action of October 17, 2006). The Examiner cites Nagaraja *et al.* as allegedly teaching that “the proteomic profiles indicated altered abundance of fewer proteins as compared to transcript profiles.” (Final Office Action of October 17, 2006).

Appellants respectfully submit that the fact that many more transcripts than proteins were found to be differentially expressed does not mean that most mRNA changes did not result in

correlating protein changes, but merely reflects the fact that expression levels were only measured at all for many fewer proteins than transcripts. In particular, the total number of proteins whose expression levels could be visualized on silver-stained gels was only about 300 (page 2332, col. 1), as compared to the approximately 14,500 genes on the microarray chips for which mRNA levels were measured. (Page 2336, col. 1). Since the expression levels of so many fewer proteins than transcripts were measured, it is hardly surprising that a smaller absolute number of proteins than mRNAs were found to be overexpressed, because the protein products of most of the overexpressed mRNAs would not have been among the small number of proteins identified on the gels.

The Examiner next cites Waghray *et al.*, to the effect that “for most of the proteins identified, there was no appreciable concordant change at the RNA level,” and that “[t]he change in intensity for most of the affected proteins identified could not be predicted based on the level of the corresponding RNA.” (Final Office Action of October 17, 2006). Appellants reiterate that they need only show that there is a correlation between mRNA and protein levels, such that mRNA overexpression generally predict protein overexpression. A showing that mRNA levels can be used to “accurately predict” the precise levels of protein expression is not required.

Appellants also emphasize that Appellants are asserting that a measurable change in mRNA level generally leads to a corresponding change in the level of protein expression, not that changes in protein level can be used to predict changes in mRNA level. Waghray et al. did not take genes which showed significant mRNA changes and check the corresponding protein levels. Instead, the authors looked at a small and unrepresentative number of proteins, and checked the corresponding mRNA levels. Waghray *et al.* acknowledge that only “[a] relatively small set of genes could be analyzed at the protein level, largely due to the limited sensitivity of 2-D PAGE.” (Page 1337, col. 1). In particular, while the authors examined the expression levels of 16,570 genes (page 1329, col. 2), they were able to measure the expression levels of only 1031 proteins. (Page 1333, col. 2). Waghray *et al.* does not teach that changes in mRNA expression were not correlated with changes in expression of the corresponding protein. All Waghray *et al.* state is that “for most of the proteins identified, there was no appreciable concordant change at the mRNA level.” (Page 1337, col. 2). This statement is not relevant to Appellants’ assertion of utility, since Appellants are not asserting that changes in mRNA levels

are the only cause of changes in protein levels. Waghray *et al.* do not contradict Appellants' assertion that changes in mRNA expression, in general, correspond to changes in expression of the corresponding protein.

Lastly, the Examiner cites Sagynaliev *et al.*, as allegedly teaching that "it is also difficult to reproduce transcriptomics results with proteomics tools." In particular, the Examiner notes that according to Sagynaliev *et al.*, of 982 genes found to be differentially expressed in human CRC, only 177 (18%) have been confirmed using proteomics technologies. (Final Office Action of October 17, 2006).

The Sagynaliev *et al.* reference, titled "Web-based data warehouse on gene expression in human colorectal cancer" (emphasis added), drew conclusions based upon a literature survey of gene expression data published in human CRC, and not from experimental data. While a literature survey can be a useful tool to assist researchers, the results may greatly over-represent or under-represent certain genes, and thus the conclusions may not be generally applicable. In particular, Appellants note that, as evidenced by Lian *et al.*, Nagaraja *et al.*, and Waghray *et al.*, discussed above, the number of mRNAs examined in transcriptomics studies is typically much larger than the number of proteins examined in corresponding proteomics studies, due to the difficulties in detecting and resolving more than a small minority of all expressed proteins on 2D gels. Thus, the fact that only 18% of all genes found to be differentially expressed in human CRC have been confirmed using proteomics technologies does not mean that the corresponding proteins are not also differentially expressed, but is most likely due to the fact that the corresponding proteins were not identified on 2D gels, and thus their expression levels remain unknown.

The authors of Sagynaliev *et al.* acknowledge the many technical problems in finding proteomic data for CRC that can be matched to transcriptomic data to see if the two correlate. The authors state that "results have been obtained using heterogeneous samples in particular cell lines, whole tissue biopsies, and epithelial cells purified from surgical specimens." However, "Results obtained in cell lines do not allow accurate comparison between normal and cancer cells, and the presence/absence of proteins of interest has to be confirmed in biopsies." (Page 3072, left column). In particular, the authors specifically note that "only a single study [1]

provided differential display protein expression data obtained in the human patient, using whole tissue biopsy.” (Page 3068, left column, second paragraph; *see also*, Table 2).

Appellants further note that Table 2 shows that 6 out of 8 published proteomics studies were done using 2-D PAGE. However, the authors state that “2-D PAGE or 2-D DIGE have well-known technological limitations ... even under well-defined experimental conditions, 2-D PAGE parallel analysis of paired CRC samples is hampered by a significant variability.” (Page 3077, left column, third paragraph.) Therefore, Appellants respectfully submit that it is well known in the art that there are problems associated with selecting only those proteins detectable by 2D gels.

Accordingly, the Examiner cannot rely on the teachings of Nagaraja *et al.*, Waghray *et al.*, Sagynaliev *et al.* to establish a *prima facie* showing of lack of utility.

**Li *et al.***

The Examiner cites new reference Li *et al.* as teaching that “68.8% of the genes showing over-representation in the genome did not show elevated transcript levels.” (Final Office Action of October 17, 2006).

Appellants respectfully point out that Li *et al.* acknowledge that their results differed from those obtained by Hyman *et al.* and Pollack *et al.* (of record), who found a substantially higher level of correlation between gene amplification and increased gene expression. The authors note that “[t]his discordance may reflect methodologic differences between studies or biological differences between breast cancer and lung adenocarcinoma.” (Page 2629, col. 1). For instance, as explained in the Supplemental Information accompanying the Li article, genes were considered to be amplified if they had a copy number ratio of at least 1.40. In the case of PRO232, as discussed in previously filed responses and in the Goddard Declaration (of record), an appropriate threshold for considering gene amplification to be significant is a copy number of at least 2.0 (which is a higher threshold). The PRO232 gene showed significant amplification of **2.056-fold to 5.28-fold, in five lung tumors** or **2.00-fold to 5.32-fold in seven colon tumors**, and thus fully meets this standard. It is not surprising that, in the Li *et al.* reference, by using a lower threshold of 1.4 for considering gene amplification, a higher number of genes not showing corresponding increases in mRNA expression were found. Nevertheless, the results of Li *et al.*

do not conclusively disprove that a gene with a substantially higher level of gene amplification, such as PRO232, would be expected to show a corresponding increase in transcript expression.

Therefore, the Patent Office has failed to meet its initial burden of proof that Appellants' claims of utility are not substantial or credible. The arguments presented by the Examiner based on references Pennica *et al.*, Konopka *et al.*, Haynes *et al.*, Hu *et al.*, Lian *et al.*, Fessler *et al.*, Gygi *et al.*, Lilley *et al.*, Lee *et al.*, King *et al.*, Wildsmith *et al.*, Nagaraja *et al.*, Sagynaliev *et al.*, Waghray *et al.*, Madoz-Gurpide *et al.*, Feroze-Merzoug *et al.*, Bustin *et al.*, Saito-Hisaminato *et al.*, do not provide sufficient reasons to doubt the statements by Appellants that PRO232 has utility as a diagnostic marker for lung or colon cancer. Appellants once again remind the Examiner that only after the Examiner has made a proper prima facie showing of lack of utility, does the burden of rebuttal shift to the Appellant. Based on the above discussions, such a showing has not been made. Accordingly, the instant rejection should be withdrawn for the Examiner's lack of establishment of a *prima facie* showing.

Moreover, Appellants acknowledge that, in certain instances, DNA/mRNA and protein levels do not correlate. In fact, Appellants have included several such references directed towards a single gene or genes that lack a correlation in their IDS filed on July 27, 2006. The references discussed in the Preliminary Amendment filed on July 27, 2006, and the arguments therein are hereby incorporated by reference for brevity. The IDS included references that studied single genes or gene families, multiple or large families of genes, and included studies that a wide variety of techniques including gene amplification and microarray. Regardless of the techniques employed, by and large, increased genes/transcripts levels mostly correlated with increased protein levels, even if accurate predictions of proteins could not be made. As discussed throughout prosecution, the law does not require the existence of a "necessary" correlation between DNA/mRNA and protein levels, or that protein levels be "accurately predicted." In fact, authors in several of the cited references (cited both, by the Examiner, and by Appellants) themselves acknowledge that there is a general correlation between protein expression and transcript levels and DNA levels, which meets the "more likely than not standard".

In summary, Appellants maintain that even though there are certain instances where a correlation, between DNA/mRNA and protein levels do not exist, in most cases, there is



generally good correlation between them, and this was collectively demonstrated in the more than 100 references submitted by the Appellants in the IDS filed on July 27, 2006.

**D. The Gene Amplification Data Establishes Credible, Substantial and Specific Patentable Utility for the PRO232 Polypeptide**

On the other hand, as discussed throughout prosecution, Appellants submit that Example 170 of the specification further discloses that, "(a)mplification is associated with overexpression of the gene product, indicating that the polypeptides are useful targets for therapeutic intervention in certain cancers such as lung, colon, breast and other cancers and diagnostic determination of the presence of those cancers." (Emphasis added). Appellants have also submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is "more likely than not" that the encoded protein will also be expressed at an elevated level.

Besides the reference, the Declaration by Dr. Paul Polakis (Polakis I - made of record in Appellants' Response filed on August 9, 2004), principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application, explains that in the course of Dr. Polakis' research using microarray analysis, he and his co-workers identified approximately 200 gene transcripts that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Appellants submit that Dr. Polakis' Declaration was presented to support the position that there is a correlation between mRNA levels and polypeptide levels. The second Declaration by Dr. Polakis (Polakis II) presented evidentiary data in Exhibit B. Exhibit B of the Declaration identified 28 gene transcripts out of 31 gene transcripts (*i.e.*, greater than 90%) that showed good correlation between tumor mRNA and tumor protein levels. As Dr. Polakis' Declaration (Polakis II - made of record in Appellants' Response filed on July 27, 2006) says "[a]s such, in the cases where we have been able to quantitatively measure both (i) mRNA and (ii) protein levels in both (i) tumor tissue and (ii) normal tissue, we have observed that in the vast majority of cases, there is a very strong correlation between increases in mRNA expression and increases in the level of protein encoded by that mRNA." Accordingly, Dr. Polakis has provided the facts to enable the Examiner to draw independent conclusions regarding protein data. Appellants further emphasize that the opinions expressed in the Polakis Declaration, including in the above quoted statement, are all based on factual findings. For instance, antibodies binding to about 30 of these tumor antigens were

prepared and mRNA and protein levels were compared. In approximately 80% of the cases, the researchers found that increases in the level of a particular mRNA correlated with changes in the level of protein expressed from that mRNA when human tumor cells are compared with their corresponding normal cells. Therefore, Dr. Polakis' research, which is referenced in his Declaration, shows that, in general, there is a correlation between increased mRNA and polypeptide levels. Hence, one of skill in the art would reasonably expect that, based on the gene amplification data of the PRO232 gene, the PRO232 polypeptide is concomitantly overexpressed in lung or colon tumors studied as well.

Appellants further note that the sale of gene expression chips to measure mRNA levels is a highly successful business, with a company such as Affymetrix recording 168.3 million dollars in sales of their GeneChip® arrays in 2004. Clearly, the research community believes that the information obtained from these chips is useful (*i.e.*, that it is more likely than not that the results are informative of protein levels).

Thus, based on the asserted utility for PRO232 in the diagnosis of selected lung or colon tumors, the reduction to practice of the instantly claimed protein sequence of SEQ ID NO: 18 in the present application (also see pages 3- 4 and Example 4, pages 149-150), the step-by-step preparation of chimeric PRO polypeptides, including those wherein the heterologous polypeptide is an epitope tag or an Fc region of an immunoglobulin (page 74, line 23 to page 75, line 5), the description of the expression of PRO polypeptides in various host cells, including *E. coli*, mammalian cells, yeast and Baculovirus-infected insect cells at least in Examples 53-56, pages 192-199, the disclosure of the step-by-step protocol for the preparation, isolation and detection of monoclonal, polyclonal and other types of antibodies against the PRO232 protein in the specification (monoclonal and polyclonal antibodies at page 139, line 32, to page 141, line 13; humanized antibodies at page 141, line 15, to page 142, line 16; antibody fragments at page 143, line 8 onwards; labeled antibodies at pages 144-145, line 16 onwards and page 146, line 33 to page 147, line 6) and the disclosure of the gene amplification assay in Example 92, the skilled artisan would know exactly how to make and use the claimed polypeptides for the diagnosis of lung or colon cancers. Appellants submit that based on the detailed information presented in the specification and the advanced state of the art in oncology, the skilled artisan would have found such testing routine and not 'undue.'

Therefore, since the instantly claimed invention is supported by either a credible, specific and substantial asserted utility or a well-established utility, one skilled in the art would know “how to make and use” the claimed invention without undue experimentation, Appellants respectfully request reconsideration and reversal of the determination of priority for Claims 44-46 and 49-51.

**ISSUE 2. Claims 44-46 and 49-51 should be entitled to the priority date of U.S. Provisional Patent Application Serial No. 60/059121, filed September 17, 1997**

The instant application has not been granted the earlier priority date of U.S. Provisional Patent Application Serial No. 60/059121, filed September 17, 1997 on the grounds that the prior 60/059121 application fails to provide a utility and lacks an enabling disclosure for the claimed invention under 35 U.S.C. §101/112, first paragraph.”

Appellants disagree and submit that, for the same reasons discussed above under Issue 1, U.S. Provisional Patent Application Serial No. 60/059121 also satisfies the utility requirements. Therefore, Appellants should be entitled to the priority date of **September 17, 1997**.

**ISSUE 3. Claims 44-46 and 49-51 are not anticipated by Rosenthal *et al.*, DE19818619-A1 (dated 10/1999)**

Claims 44-46 and 49-51 remain rejected under 35 U.S.C. §102(b) as being anticipated by Rosenthal *et al.*, DE19818619-A1 (dated 10/1999).

For the reasons discussed above under Issue 2, Appellants maintain that they are entitled to an effective filing date of September 17, 1997 based on a properly claimed priority to International application PCT/US98/18824. Therefore, Rosenthal *et al.* is not prior art and does not anticipate the instant claims. Accordingly, this rejection under 35 U.S.C. §102(b) should be withdrawn.

**CONCLUSION**

For the reasons given above, Appellants submit that present specification and the specification of U.S. Provisional Patent Application Serial No. 60/059121 dated September 17, 1997 clearly describes and provides at least one patentable utility for the instantly claimed invention. Moreover, it is respectfully submitted that the present specification clearly teaches “how to use” the presently claimed polypeptide based upon this disclosed patentable

utility. Accordingly, Rosenthal *et al.*, DE19818619-A1 is not prior art. As such, Appellants respectfully request reconsideration and reversal of the outstanding rejection of Claims 44-46 and 49-51.

The Commissioner is authorized to charge any fees which may be required, including extension fees, or credit any overpayment to Deposit Account No. 08-1641 (referencing Attorney's Docket No. 39780-1618 P2C18).

Respectfully submitted,

Date: September 24, 2007

By: J.P. Bernhardt  
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## **VIII. CLAIMS APPENDIX**

### **Claims on Appeal**

44. An isolated polypeptide comprising:
- (a) the amino acid sequence of the polypeptide of SEQ ID NO:18;
  - (b) the amino acid sequence of the polypeptide of SEQ ID NO:18, lacking its associated signal peptide; or
  - (c) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209250;
- wherein, the nucleic acid encoding said polypeptide is amplified in lung or colon tumors.
45. The isolated polypeptide of Claim 44 comprising the amino acid sequence of the polypeptide of SEQ ID NO:18.
46. The isolated polypeptide of Claim 44 comprising the amino acid sequence of the polypeptide of SEQ ID NO:18, lacking its associated signal peptide.
49. The isolated polypeptide of Claim 44 comprising the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209250.
50. A chimeric polypeptide comprising a polypeptide according to Claim 44 fused to a heterologous polypeptide.
51. The chimeric polypeptide of Claim 50, wherein said heterologous polypeptide is an epitope tag or an Fc region of an immunoglobulin.

## IX. EVIDENCE APPENDIX

1. Declaration of Audrey Goddard, Ph.D. under 35 C.F.R. §1.132, with attached Exhibits A-G:
  - A. Curriculum Vitae of Audrey D. Goddard, Ph.D.
  - B. Higuchi, R. *et al.*, "Simultaneous amplification and detection of specific DNA sequences," *Biotechnology* 10:413-417 (1992).
  - C. Livak, K.J., *et al.*, "Oligonucleotides with fluorescent dyes at opposite ends provide a quenched probe system useful for detecting PCR product and nucleic acid hybridization," *PCR Methods Appl.* 4:357-362 (1995).
  - D. Heid, C.A. *et al.*, "Real time quantitative PCR," *Genome Res.* 6:986-994 (1996).
  - E. Pennica, D. *et al.*, "WISP genes are members of the connective tissue growth factor family that are up-regulated in Wnt-1-transformed cells and aberrantly expressed in human colon tumors," *Proc. Natl. Acad. Sci. USA* 95:14717-14722 (1998).
  - F. Pitti, R.M. *et al.*, "Genomic amplification of a decoy receptor for Fas ligand in lung and colon cancer," *Nature* 396:699-703 (1998).
  - G. Bieche, I. *et al.*, "Novel approach to quantitative polymerase chain reaction using real-time detection: Application to the detection of gene amplification in breast cancer," *Int. J. Cancer* 78:661-666 (1998).
2. Declaration of Avi Ashkenazi, Ph.D. under 35 C.F.R. §1.132, with attached Exhibit A (Curriculum Vitae).
3. Declaration of Paul Polakis, Ph.D. under 35 C.F.R. §1.132 (Polakis I).
4. Declaration of Paul Polakis, Ph.D. under 35 C.F.R. §1.132 (Polakis II).
5. Haynes *et al.*, "Proteome analysis: Biological assay or data archive?" *Electrophoresis* 19:1862-1871 (1996).
6. Rosenthal *et al.*, DE19818619-A1 (dated October 28, 1999).
7. Hyman, E., *et al.*, "Impact of DNA Amplification on Gene Expression Patterns in Breast Cancer," *Cancer Research* 62:6240-6245 (2002).
8. Pollack, J.R., *et al.*, "Microarray Analysis Reveals a Major Direct Role of DNA Copy Number Alteration in the Transcriptional Program of Human Breast Tumors," *Proc. Natl. Acad. Sci. USA* 99:12963-12968 (2002).
9. Hanna *et al.*, "HER-2/neu Breast Cancer Predictive Testing," Pathology Associates Medical Laboratories (1999).
10. Konopka *et al.*, "Variable Expression of the Translocated c-abl oncogene in Philadelphia-chromosome-positive B-lymphoid cell lines from chronic myelogenous leukemia patients" *Proc. Natl. Acad. Sci. USA* 83: 4049-52, (1986).

11. Hu *et al.*, "Analysis of genomic and proteomic data using advanced literature mining," *J. Proteome Res.* 2: 405-412 (2003).
12. Lian *et al.*, "Genomic and proteomic analysis of the myeloid differentiation program," *Blood* 98: 513-524 (2001).
13. Fessler *et al.*, "A genomic and proteomic analysis of activation of the human neutrophil by lipopolysaccharide and its mediation by p38 mitogen-activated protein kinase," *J. Biol. Chem.* 277: 31291-31302 (2002).
14. Abe, N., *et al.*, *Br J Cancer* - 89(11):2104-9 (2003).
15. Alberts, B., *et al.*, *Molecular Biology of the Cell* (3rd ed. 1994) Cell 3rd at 453 Figure 9-2 of Cell 3rd Cell 3rd at 403.
16. Alberts, B., *et al.*, *Molecular Biology of the Cell* (4rd ed.) In Cell 4th, Figure 6-3 on page 302 Figure 6-90 on page 364 of Cell 4th Cell 4th at 364 Cell 4th at 379.
17. Ando, M., *et al.*, *Br J Haematol.*, - 130(6):860-8 (2005).
18. Aust, G., *et al.*, *Thyroid* - 7(5):713-24 (1997).
19. Barnes, V.L., *et al.*, *J Histochem Cytochem.* - 47(6):787-98 (1999).
20. Bea, S., *et al.*, *Cancer Res.* - 61(6):2409-12 (2001).
21. Beer, *et al.*, *Nature Medicine* - 8(8):816-824 (2002).
22. Blaschke, V., *et al.*, *J Immunol Methods.* - 246(1-2):79-90 (2000).
23. Buckley, A.R., *et al.*, *Apoptosis.* - 2(6):518-28 (1997).
24. Caberlotto, L. *et al.*, *Neurosci Lett.* - 265(3):191-4 (1999).
25. Caberlotto, L., *et al.*, *Eur J Neurosci.* - 17(9):1736-46 (2003).
26. Choi, D., *et al.*, *J Soc Gynecol Investig.* - 9(1):41-6 (2002).
27. Couvelard, A., *et al.*, *Virchows Arch.* - 445(3):279-84 (2004).
28. Dagenais, A., *et al.*, *Am J. Physiol Lung Cell Mol Physiol.* - 286(2):L301-11 (2004).
29. De Boer, C.J., *et al.*, *Ann Oncol.* - 7(3):251-6 (1996).
30. Debieve, F., *et al.*, *Mol Hum Reprod.* - 6(8):743-9 (2000).
31. Dong, Z., *et al.*, *Invest Ophthalmol Vis Sci* - 42(13):3223- (2001).
32. Duchrow, M., *et al.*, *Cancer Invest.* - 19(6):588-96 (2001).

33. Dyer, J., *et al.*, Equine Vet J. - 34(4):349-58 (2002).
34. Egwuagu, C.E., *et al.*, J Immunol. - 168(7):3181-7 (2002).
35. El-Ghrably, I.A., *et al.*, Br J Ophthalmol. - 85(4):461-70 (2001).
36. Eleore, L., *et al.*, Neuroscience - 136(1):147-60 (2005).
37. Forsberg, H., *et al.*, Free Radic Res. - 24(6):451-9 (1996).
38. Freyschuss, B., *et al.*, Endocrinology - 133(4):1548-54 (1993).
39. Fu, K., *et al.*, Blood - 106(13):4315-21 (2005).
40. Fuchs, A.R., *et al.*, Biol Reprod. - 54(3):700-8 (1996).
41. Furuta, J., *et al.*, Melanoma Res. - 15(1):15-20 (2005).
42. Futcher, B., *et al.*, Mol Cell Biol., - 19(11):7357-68 (1999).
43. George, J., *et al.*, Biochem Pharmacol. - 49(7):873-81 (1995).
44. Giroux, M., *et al.*, J Immunol. - 165(7):3985-91 (2000).
45. Gnatenko, D.V., *et al.*, Blood - 101(6):2285-93 (2003).
46. Godbout, R., *et al.*, J Biol Chem, - 273(33):21161-8 (1998).
47. Goldenberg, R.C., *et al.*, J Endocrinol. - 177(2):327-35 (2003).
48. Golebiowski, F., *et al.*, Acta Biochim Pol. - 50(4):1065-73 (2003).
49. Greenbaum, D., *et al.*, BioinformaticsI - 18(4):585-496 (2002).
50. Grem, J.L., *et al.*, Clin Cancer Res. - 7(4):999-1009 (2001).
51. Grenback, E., *et al.*, Regul Pept, - 117(2):127-39 (2004).
52. Gromova, I., *et al.*, Int J. Oncol. - 13(2):379-83 (1998).
53. Guo, Y., *et al.*, Zhinghua Jie He He Hu Xi Za Zhi - 25(6):337-40 (2002).
54. Habu, Y., *et al.*, Biochem Pharmacol - 69(6):993-9 (2005).
55. Hahn, M.E., *et al.*, Toxicol Appl Pharmacol. - 127(2):187-98 (1994).
56. Hähnel, E., *et al.*, Breast Cancer Research and Treatment - 24:71-74 (1992).



57. Hamilton, L.M., *et al.*, Clin Exp Allergy. - 33(2):233-40 (2003).
58. Hassett, C., *et al.*, Arch Biochem Biophys. - 337(2):275-83 (1997).
59. Hirsch, F.R., *et al.*, Clinical Cancer Research - 7:5-22 (2001).
60. Holten-Andersen, M.N., *et al.*, Int J Cance, - 113(2):198-206 (2005).
61. Huang, Y.H., *et al.*, J Med Virol. - 70(4):610-6 (2003).
62. Huettnner, P.C., *et al.*, Mod Pathol. - 5(3):250-6 (1992).
63. Hui, P., *et al.*, Leuk Lymphoma. 44(8):1385-94 (2003).
64. Husain, I., *et al.*, Cancer Res. - 54(2):539-46 (1994).
65. Ihmann, T., *et al.*, J Cancer Res Clin Oncol. - 130(12):749-56 (2004).
66. Ikegami, T., *et al.*, Am J Physiol Cell Physiol. - 281(4):C1396-402 (2001).
67. Jacquemin, E., *et al.*, Int J Biol. - 37(3):417-23 (1993).
68. Jaime, M., *et al.*, Hepatology - 35(5):1063-71 (2002).
69. Janssens, N., *et al.*, Tumour Biol. - 25(4):161-71 (2004).
70. Jungbluth, A.A., *et al.*, Int J. Cancer - 92(6):856-60 (2001).
71. Kalabis, G.M., *et al.*, Biol Reprod. - 73(4):591-7 (2005).
72. Kammaori, M., *et al.*, Int J Oncol. - 27(5):1257-63 (2005).
73. Khal, J., *et al.*, Br J Cancer - 93(7):774-80 (2005).
74. Khal, J., *et al.*, Int J. Biochem Cell Biol. - 37(10):2196-206 (2005).
75. Kogo, H., *et al.*, J Biol Chem. - 279(24):25574-81 (2004).
76. Kommoss, F., *et al.*, Acta Obstet Gynecol Scand Suppl. - 155:19-24 (1992).
77. Kumar, U., *et al.*, Breast Cancer Res. Treat. - 92(2):175-86 (2005).
78. Kuo, C.C., *et al.*, Proteomics - 5(4):894-906 (2005).
79. Landmark, B.F., *et al.*, J Reprod Fertil. - 99(2):323-34 (1993).
80. Lassmann, S., *et al.*, J Pathol. - 198(2):198-206 (2002).

81. Legrand, O., *et al.*, Br J, Haematol. - 94(1):23-33 (1996).
82. Lemstrom, K.B., *et al.*, Circulation - 105(21):2524-30 (2002).
83. Lewin, B., Genes VI Genes VI at 847-848 (1997).
84. Li, Y., *et al.*, Invest Ophthalmol Vis Sci. - 44(3):1299-304 (2003).
85. Li, Z.B., *et al.*, Biochem Biophys Res Commun. - 327(4):1163-9 (2005).
86. Lindberg, P., *et al.*, Arch Oral Biol. - 46(1):23-31 (2001).
87. Macabeo-Ong, M., *et al.*, 15(9):979-87 (2002).
88. Maruyama, H., *et al.*, Am J Pathol. - 155(3):815-22 (1999).
89. Meehan, T.P., *et al.*, J Mol Endocrinol. - 32(1):247-55 (2004).
90. Mendoza-Rodriguez, C.A., *et al.*, Mol Reprod Dev. 64(4):379-88 (2003).
91. Meoni, P., *et al.*, Brain Res Mol Res. - 54(1):13-23 (1998).
92. Meric, F., *et al.*, Molecular Cancer Therapeutics - 1:971-979 (2002).
93. Mezzano, S.A., *et al.*, Kiney Int. - 57(1):147-58 (2000).
94. Mingrone, G., *et al.*, Obes Res. - 11(5):632-40 (2003).
95. Miralles, C.P., *et al.*, Brain Res Mol Res. - 24(1-4):129-39 (1994).
96. Mizrachi, D., *et al.*, Biol Reprod. - 61(3):776-84 (1999).
97. Monaghan, P., *et al.*, J Gen Virol. - 86(Pt 10):2769-80 (2005).
98. Montuori, N., *et al.*, Int J Cancer - 105(3):353-60 (2003).
99. Munaut, C., *et al.*, Int J Cancer - 106(6):848-55 (2003).
100. Nie, Y., *et al.*, Carcinogenesis - 22(10):1615-23 (2001).
101. Nuciforo, P.G., *et al.*, Hum Pathol. - 34(7):639-45 (2003).
102. Oberringer, M., *et al.*, Biochem Biophys Res Commun. - 214(3):1009-14 (1995).
103. Orntoft, T.F., *et al.* Molecular & Cellular Proteomics – 1:37-45 (2002).
104. Pachmann, K., *et al.*, Br J. Haematol - 112(3):749-59 (2001).

105. Pairon, J.C., *et al.*, Am J Respir Cell Mol Biol. - 11(4):386-96 (1994).
106. Papotti, M., *et al.*, Diagn Mol Pathol. - 9(1):47-57 (2000).
107. Papotti, M., *et al.*, Virchows Arch. - 440(5):461-75 (2002).
108. Paredes, J., *et al.*, Clin Cancer Res. - 11(16):5869-77 (2005).
109. Politis, I., *et al.*, J Dairy Sci. - 75(6):1423-9 (1992).
110. Preesman, A.H., *et al.*, J Invest Dermatol. - 99(5):587-93 (1992).
111. Pullig, O., *et al.*, Osteoarthritis Cartilage - 10(4):253-63 (2002).
112. Rey, C., *et al.*, Biochem Pharmacol. - 60(11):1636-46 (2000).
113. Rudlowski, C., *et al.*, Am J. Clin Pathol. - 120(5):691-8 (2003).
114. Sasaki, T., *et al.*, Exp Cell Res. - 275(2):189-99 (2002).
115. Sedelies, K.A., *et al.*, J Biol Chem. - 279(25):26581-7 (2004).
116. Shen, Y., *et al.*, Blood - 104(9):2936-9 (2004).
117. Shinohara, Y., *et al.*, Biochim Biophys Acta - 1368(1):129-36 (1998).
118. Silvers, A.L., *et al.*, Photochem Photobiol. - 75(3):302-10 (2002).
119. Song, L., *et al.*, Am J. Physiol. - 267(4 Pt 2):F546-57 (1994).
120. Spaziani, E.P., *et al.*, J Interferon Cytokine Res. - 18(12):1039-44 (1998).
121. Spika, I., *et al.*, Skin Pharmacol Appl Skin Physiol. - 16(3):143-50 (2003).
122. Splinter, P.L., *et al.*, J Biol Chem - 278(8):6268-74 (2003).
123. Stearns, M.E., *et al.*, Cancer Res. - 53(4):878-83 (1993).
124. Stein, R., *et al.*, J Urol. - 164(3Pt 2):1026-30 (2000).
125. Strickland, I., *et al.*, J Invest Dermatol. - 108(5):763-8 (1997).
126. Strutz, F., *et al.*, Kidney Int. - 57(4):1521-38 (2000).
127. Takahashi, K., *et al.*, J Biol. Chem. - 278(47):46654-60 (2003).
128. Takimoto, Y., *et al.*, Circulation - 105(4):490-6 (2002).

129. Telek, G., *et al.*, J Surg Res. - 96(1):56-67 (2001).
130. Timchenko, L., *et al.*, Semin Cell Biol. - 6(1):13-9 (1995).
131. Torronen, R., *et al.*, Chem Biol. Interact. - 83(2):107-19 (1992).
132. Ullmannova, V., *et al.*, Leuk Res. - 27(12):1115-23 (2003).
133. Van Beers, E.H., *et al.*, J Histochem Cytochem. - 46(2):231-40 (1998).
134. Van Der Wilt, C.L., *et al.*, Eur J Cancer - 39(5):691-7 (2003).
135. Waldherr, R., *et al.*, Pediatr Nephrol. - 7(4):471-8 (1993).
136. Walmer, D.K., *et al.*, Cancer Res. - 55(5):1168-75 (1995).
137. Wang, J., *et al.*, Cancer Res. - 54(2):560-4 (1994).
138. Wang, J., *et al.*, Urol Res. - 28(5):308-15 (2000).
139. Wang, L.G., *et al.*, Cancer Res. - 57(4):714-9 (1997).
140. Weterman, M.A., *et al.*, Cancer Res. - 53(24):6061-6 (1993).
141. Williams, E.T., *et al.*, J Pharmacol Exp Ther. 311(2):728-35 (2004).
142. Wojtaszek, P.A., *et al.*, Oncogene - 8(3):755-60 (1993).
143. Zhigang, Z., *et al.*, World Journal of Surgical Oncology - 2-13 (2004).
144. Zhong, W., *et al.*, Free Radic Biol Med. - 27(11-12):1334-45 (1999).
145. Xi, L., *et al.*, Zhonghua Fu Chan Ke Za Zhi - 40(6):407-10 (2005).
146. Bustin *et al.*, (2002) Trends in Mol. Med., 8(6): 269-272.
147. Lilley *et al.*, "Proteomics" Mol. Biol. in Cellular Path. (2003) England: John Wiley & Sons, p 351-352.
148. Lee *et al.*, (2000) Proc. Nat. Acad. Sci., USA, 97(18): 9834-39.
149. King *et al.*, 2001, J. Am. Med. Assoc. 286: 2280-2288.
150. Wildsmith *et al.*, "Gene Expression Analysis using Microarrays" Mol. Biol in Cellular Path. (2003) England: John Wiley & Sons, p 269-286.
151. Nagaraja *et al.*, 2006, Oncogene 25: 2328-2338.

152. Waghray *et al.*, 2001, Proteomics, 1: 1327-1338.
153. Sagynaliev *et al.*, 2005, Proteomics, 5: 3066-3076.
154. Feroze-Merzoug *et al.*, (2001), Cancer and Metastasis Rev., 20:165-171.
155. Madoz-Gurpide *et al.*, 2003, Adv. Exp. Med. Biol., 532:51-58.
156. Saito-Hisaminato *et al.*, (2002), DNA Research, 9:35-45.
157. Gygi *et al.*, (1999), Mol. and Cell Biol., 19: 1720-30.
158. Li *et al.*, 2006, Oncogene, 25: 2628-2635.

Item 1 was submitted with Appellants' Response filed July 25, 2005, and were considered by the Examiner as indicated in the second Final Office action mailed October 21, 2005.

Item 2 was submitted with Appellants' Response filed December 10, 2003, and was considered by the Examiner as indicated in the Office action mailed April 8, 2004.

Items 3, 103 and 7-9, were submitted with Appellants' Response filed August 9, 2004, and were considered by the Examiner as indicated in the Office action mailed December 6, 2004.

Item 4 was submitted with Appellants' Response filed July 27, 2006, and was considered by the Examiner as indicated in the Final Office Action mailed October 17, 2006.

Item 1 (E), *i.e.*: Pennica *et al.*, and Items 5-6 were made of record by the Examiner in the Office Action mailed September 29, 2003.

Items 10-11 were made of record by the Examiner in the Office Action mailed February 23, 2005.

Items 12-13 were made of record by the Examiner in the Final Office Action mailed October 21, 2005.

Items 14-145 were submitted with Appellants' Response filed July 27, 2006, and were considered by the Examiner as indicated in the Final Office Action mailed October 17, 2006.

Items 146-158 were made of record by the Examiner in the Final Office Action mailed October 17, 2006.

**X. RELATED PROCEEDINGS APPENDIX**

None - no decision rendered by a Court or the Board in any related proceedings identified above.